REMARKS

Claims 1, 2, 5-8 are pending. Claims 9-13, 15, 18-35, and 37-49 are withdrawn as directed to a non-elected invention. Claims 9-13, 15, 18-35, and 37-49 have been cancelled without prejudice and may be presented in a continuation or a divisional application. Claims 7 and 8 have been amended solely to correct the antecedent basis and not because of any prior art cited by the Office. Claim 1 has been amended to correct a typographical error. Upon entry of this amendment, claims 1, 2, and 5-8 will be pending and subject to examination.

No new matter has been added and Applicant respectfully requests that the amendment be entered.

Interview Summary

Applicants thank Examiner Jeffrey Parkin for taking the time to discuss the present application on July 10, 2007, in a telephone interview with the undersigned representative. The present outstanding rejection was discussed. The response incorporates the suggestions of the Examiner.

Supplemental Information Disclosure Statement

Applicants submit herewith a supplemental information disclosure statement citing U.S. Application No. 10/901,399, entitled "Lipoparticles comprising proteins, methods of making, and using the same." Applicants have also cited in the Supplemental Information Disclosure statement the most recent Office Action issued in 10/901,399 and the references cited therein.

Withdrawn Rejections

The pending claims were previously rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to adequately describe the present invention to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants had previously argued in responses to the Office and the Applicants Arguments accompanying Pre-Appeal Brief Conference Request, filed December 18,

2006, that the application satisfied the written description requirement. In response to these submissions Applicants acknowledge that the rejection under 35 U.S.C. § 112, first paragraph has been withdrawn because the pending claims satisfy the written description requirement and demonstrate possession of the claimed invention at the time the application was filed.

New Rejection under 35 U.S.C. § 103

Claims 1, 2, and 5-8 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Schubert *et al.* (*Journal of Virology*, Vol. 66, No. 3, p. 1579-1589, (1992)) in view of Choe *et al.* (*Cell,* Vol. 85, pp. 1135-1148 (1996)). The Office alleges that the Schubert reference discusses vesicular stomatitis virus particles comprising CD4, a single-transmembrane membrane protein. As acknowledged by the Examiner, the Schubert reference fails to disclose a virus-like particle as described in the pending claims that include a heterologous multiple membrane spanning protein. According to the Examiner, the Choe reference discusses that CD4 and CCR5 are required for infectivity of primary HIV-1 isolates. Therefore, according to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art to express both CD4 and CCR5 in the VSV particles disclosed in the Schubert reference since it "would facilitate the targeting of HIV-infected cells." Applicants respectfully disagree because one of skill in the art would not have had a reason to combine the references. Further, if the references had been combined the results achieved by the claimed invention would not have been predictable, which rebuts any *prima facie* obviousness rejection.

The combination of claimed elements is not obvious when the result of the combination is not predictable. *See KSR Int'l Co. v. Teleflex Inc*, 127 S. Ct. 1727, 1739 (2007). When elements known in the prior art are combined and work together in "an unexpected and fruitful manner" the claimed invention is not obvious. *Id.* at 1740. The Court further explained that when a combination does something that is unexpected or unpredictable the claimed invention is not obvious. *Id.* The Court explained that one must ask whether an invention "is more than the predictable use of prior art elements according to their established functions." *Id.* The Court

also cautioned that the obviousness review should be explicit and should not be supported by merely "conclusory statements." *Id.* at 1741.

Additionally, the presence of elements in the prior art is not sufficient for a combination to be rejected as obvious. The Court in *KSR* explained that "most, if not all" inventions rely upon elements present in the prior art and, therefore, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* The reason need not be explicit in the literature (*i.e.*, patents or scientific), but can be from other sources such as "market demand." *Id.* Further, the court explained that the standard of obvious to try may be sufficient in finding an invention obvious where the combination leads to the "anticipated" or predictable success. *Id.* at 1742. Thus, an invention that produces results that are unpredictable or achieves unexpected results indicates that the claimed invention is not obvious.

The claimed particles are not obvious because the Office has not supplied a sufficient reason why the references would be combined. Additionally, even if there were a reason for a proper combination, the particles are not obvious because success was unpredictable and the claimed particles yielded unexpected results.

The Office's reason why the Schubert and Choe references would be combined is not sufficient to support a *prima facie* obviousness rejection. The Schubert reference discusses insertion of the HIV CD4 receptor into the envelope of vesicular stomatitis virus (VSV) particles. CD4 is a single-transmembrane membrane spanning protein. The Schubert article does not discuss or provide a reason to insert a heterologous multiple membrane spanning protein into a VSV particle or a particle as claimed. According, to the Office, the Choe reference fills the void left by the Schubert reference because "Choe and associates clearly demonstrate that both CD4 and CCR5 are required for the infectivity of primary HIV-1 isolates." (Office Action, page 2). Based on this result the Office alleges that "it would have been *prima facie obvious* . . . to express both CD4 and CCR5 [in a particle] . . . since this would facilitate their targeting to HIV-infected cells" because it would "enable the skilled artisan to deliver therapeutic or other agents to the cell of interest." (Office Action, page 2). Applicants respectfully disagree with the reason provided by the Office.

Even though the Schubert reference discloses a VSV particle incorporating CD4 into and Choe discloses that CCR5 and CD4 are required for HIV infectivity, the leap made by the Office that it would have led one of ordinary skill in the art to insert a heterologous multiple membrane spanning protein into a particle as described in Schubert because it would "enable the skilled artisan to deliver therapeutic or other agents to the cell of interest" is not supported by the objective evidence. The Choe reference fails to disclose or suggest that inserting a heterologous CCR5, a multiple membrane spanning protein, into a particle would facilitate the targeting of a particle into a cell as the Examiner alleges. In contrast, the Choe reference explains that the CCR5 presence on the cell, not the particle, enhances the ability of HIV viral particles to infect a cell expressing CD4 and CCR5. Expressing CCR5 in a particle, therefore, would not enhance its entry into the cell since the presence of CCR5 is required to be on the cell not the particle. Accordingly, the reason supplied by the Office is not supported by the references cited. Therefore, the present invention is not *prima facie* obvious.

Even if one of skill in the art would have had a reason to combine the Choe and Schubert references, one of skill in the art could not have predicted the success or outcome of such combination. Because one of skill in the art could not have predicted success the present invention is not obvious. *See KSR*, 127 S. Ct. at 1739-42. Furthermore, an invention is not obvious if one of ordinary skill in the art has no reasonable expectation of success when combining the prior art references or elements. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). A reasonable expectation of success does not require "absolute predictability," but it does require that there is a "reasonable expectation that the . . . result will be achieved." *In re Merck & Co.*, 800 F.2d 1091, 1097, 2321 U.S.P.Q. 375, 379 (Fed. Cir. 1986).

Recently the Court of Appeals for the Federal Circuit also evaluated what is meant by a reasonable expectation of success in *Pharmastem Therapuetics, Inc. v. Viacell, Inc.*, 05-1490,-1551 (Fed. Cir. July 9, 2007). In *Pharmastem*, the invention at issue was directed to stem cells derived from cord blood that are present in an amount sufficient to effect hematopoietic reconstitution of a human adult and a method for hematopoietic or immune reconstitution of a human using the same. *Id.* at *4-5. In *Pharmastem,* the Federal Circuit reviewed the prior art and found that there was a strong suspicion that human cord blood contained stem cells in an

amount that would satisfy the claims but that the prior art did not conclusively prove what was "strongly suspected." *Id.* at *36. The Federal Circuit concluded that the inventors of the claimed invention had done nothing more than "merely [use] routine research methods to prove what was already believed to be the case." *Id.*

Here, there was no strong suspicion or a reasonable expectation of success that one could incorporate heterologous multiple membrane spanning proteins into the virus-like particles based on the prior art at the time of the invention. Rather, there was no expectation of success that one could incorporate heterologous multiple membrane spanning proteins into virus-like particles at the time of the invention. For example, in Hoxie *et al.* (Nonrandom Association of Cellular Antigens with HTLV-III Virions, *Human Immunology*, Vol. 18, pp. 39-52 (1987)) the authors stated that there is a "nonrandom process in which some . . . antigens are selectively incorporated into the viral envelope." *Hoxie* at p. 47, first full paragraph. Hoxie demonstrates that certain HLA antigens are selectively incorporated into HTLV-III (HIV-1) virions. Because the virions selectively incorporate only certain cellular proteins there could be no reasonable expectation of success that heterologous multiple membrane spanning proteins could be incorporated into a virus-like particle as described in the pending claims.

Furthermore in Ott (Cellular Proteins in HIV Virions, *Medical Virology*, Vol 7, pp. 167-80 (1997)) the author stated "it has been a general observation that enveloped viruses appear to exclude cellular surface proteins from the budding virion." *Id.* at 169, right column, first full paragraph. Ott discusses proteins that have been found to be incorporated naturally, i.e. not heterologous proteins, by HIV Virions. Ott includes a table on p. 172 that lists 33 proteins that are incorporated naturally by HIV. Of these 33 proteins, 32 are single-transmembrane proteins. Only one, CD63, is a multiple membrane spanning protein. However, CD63 was not expressed heterologously and the article also does not provide a reasonable expectation of success that expressing multiple membrane spanning proteins heterologously would lead to their incorporation into the claimed particles. On the contrary, the fact that only 1 of 33 cellular proteins found on HIV virions was a multiple membrane spanning protein suggests that multiple membrane spanning proteins would not be expected to be readily incorporated onto the surface of viral membranes.

Further evidence that the incorporation of proteins into particles is selective and, therefore, would not provide one of skill in the art with an expectation of success is a showing that CD4 is selectively incorporated into Avian Leukosis Virus (ALV) particles. See Young *et al.*, Efficient Incorporation of Human CD4 Protein into Avian Leukosis Virus Particles, *Science*, Vol. 250, pp. 1421-23 (1990). In Young, the authors studied the incorporation of proteins into ALV particles. The authors found that CD4 could be incorporated into ALV particles, just as Schubert had found that CD4 could be incorporated into VSV particles. The Young reference also tested the incorporation of other proteins into ALV particles and found that the incorporation was selective. The authors stated "the inefficient incorporation of other quail cell glycoproteins into virions . . . demonstrates that CD4 is selectively taken up by ALV." *Id.* at 1422, left column, bottom of second full paragraph.

In Schnell *et al.* (Foreign Glycoproteins Expressed from Recombinant Vesicular Stomatitis Viruses are Incorporated Efficiently into Virus Particles, *P.N.A.S.*, Vol. 93, pp. 11359-11365 (1996)), the authors found that the physical properties of the proteins being incorporated is also important and can be detrimental to their ability of being incorporated into virus particles. *See id.* at 11364, left column, last paragraph. Schnell explains that proteins that are excluded from VSV particles are "presumably excluded . . . because of steric constraints such as large cytoplasmic domains, association with large cytoplasmic proteins or association with domains enriched in specific lipids." *Id.* Schnell also states that "the amount of space available for foreign proteins [non-VSV proteins] may be limited." *Id.* at 11364, right column, first full paragraph. Accordingly, based on Schnell one of skill in the art would not have had an expectation of success of being able to incorporate multiple membrane spanning proteins into the particles.

The above references demonstrate that prior to the invention there was no expectation of success for incorporation of multiple-spanning membrane proteins into virus-like particles. The underlying biology behind this expectation was that multiple membrane spanning proteins are proteins that would have steric constraints, be associated with specific lipids, and associate with large cytoplasmic proteins because of their importance in cell signaling. In addition, multiple-spanning membrane proteins usually lose their structure and function outside of their native lipid

environment. In contrast, single membrane spanning proteins, such as CD4, do not have the same steric constraints as multiple membrane spanning proteins and usually do not require a lipid bilayer to retain their structure and function. Compared to cells, enveloped viruses have very different lipid curvature, lipid content, and internal protein structures that were expected to influence the ability of multiple-spanning membrane proteins to be incorporated and maintain their structure and function.

Therefore, because of the differences between multiple membrane spanning proteins and single membrane spanning proteins and the factors described above, one of ordinary skill in the art would not have had a reasonable expectation of success to yield the presently claimed invention even if the references were combined.

The present set of facts is in contrast to those in *Pharmastem*, which is discussed above. In *Pharmastem*, the prior art suggested that cord blood contained stem cells but that fact had not been proven conclusively. *Pharmastem* at *36. Here, there is no suggestion that virus-like particles, such as those claimed, would incorporate heterologous multiple membrane spanning proteins. Here, unlike in *Pharmastem*, the prior art suggests that the incorporation could work with a single membrane spanning protein, but was silent regarding a heterologous multiple membrane spanning protein. Therefore, the present application does more than use routine experimentation to verify what was strongly suspected. Instead, the present application describes and enables an invention that previously did not have a reasonable expectation of success.

Accordingly, because one of ordinary skill in the art would not have a reasonable expectation of success the pending claims are not obvious.

The present invention is also not obvious because of the unexpected results that the heterologous multiple membrane proteins retain their structure and function in the claimed particles. If an invention achieves unexpected or surprising results, such results can also be used to rebut a *prima facie* obviousness rejection. *See* M.P.E.P. § 2141. The unexpected results achieved with the present invention are that the multiple membrane spanning proteins preserve their biological function in the virus-like particles, which allows them to be studied. The specification states that prior to the present invention "production of virus particles comprising

host cell receptors or other surface proteins while preserving the biological function of the molecule, has not been achieved." (Specification, ¶11).

As set forth in a declaration by Dr. Benjamin Doranz, submitted herewith, it was surprising that the heterologous multiple membrane spanning proteins in the claimed particles retained their biological function. (Doranz Declaration, ¶ 6). The declaration by Dr. Doranz states that four ion channels, which are multiple membrane spanning proteins, have been incorporated into the claimed particles and that the ion channels retain their function. (Doranz Declaration, ¶ 3). Dr. Doranz also states that G-protein coupled receptors incorporated into virus-like particles function in the VLPs. (Doranz Declaration, ¶ 4). Dr. Doranz also states that the multiple membrane proteins are still able to bind their ligand. (Doranz Declaration, ¶ 5). These results were surprising and not expected. (Doranz Declaration, ¶ 6). These results demonstrate that not only was the incorporation of multiple membrane spanning proteins unexpected but it was further surprising that the proteins when incorporated in a non-cellular environment retain their structure and function. Dr. Doranz states that these surprising results allow heterologous multiple membrane proteins to be used and studied in ways that prior to the present invention were not possible. (Doranz Declaration, ¶ 7).

Therefore, the unexpected results that claimed virus-like particles can incorporate functional heterologous multiple membrane spanning proteins is further evidence demonstrating the present invention is non-obvious.

Accordingly, because one of skill in the art would not have had a reason to combine the references, and even if the references were combined there would not have been an expectation of success the present invention is not obvious. Furthermore, the obviousness rejection should be withdrawn because of the surprising result that the heterologous multiple membrane proteins incorporated into the particles are folded properly and functional. Thus, claims 1, 2, and 5-8 are patentable and non-obvious. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Applicants respectfully assert that the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 963-5107 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Enclosures:
1. Declaration under 1.132 by Dr. Benjamin Doranz
2. Schnell *et al.* (Foreign Glycoproteins Expressed from Recombinant Vesicular Stomatitis Viruses are Incorporated Efficiently into Virus Particles, *P.N.A.S.*, Vol. 93, pp. 11359-11365 (1996)).
3. Hoxie *et al.* (Nonrandom Association of Cellular Antigens with HTLV-III Virions, *Human Immunology*, Vol. 18, pp. 39-52 (1987)).
4. Young *et al.*, Efficient Incorporation of Human CD4 Protein into Avian Leukosis Virus Particles, *Science*, Vol. 250, pp. 1421-23 (1990).
5. Ott (Cellular Proteins in HIV Virions, *Medical Virology*, Vol 7, pp. 167-80 (1997)).